Briefly, the present invention relates to a method for reducing neuronal degeneration in the central nervous system or peripheral nervous system of an individual in need thereof by causing NS-specific activated T cells to accumulate at the site of neuronal degeneration in the individual in need. By causing such T cell accumulation at the site of injury or disease, neuronal degeneration at that site is reduced. The claims exclude the situation where the individual has an autoimmune disease and the T cells are activated against the autoimmune antigen involved in that disease. Preferably, the NS-specific activated T cells are caused to accumulate at the site of neuronal degeneration by administering NS-specific activated T cells (passive immunization) or an NS-specific antigen, a peptide derived therefrom or a nucleotide sequence encoding such an antigen or peptide (active immunization).

The restriction requirement in this case has been made final. Claims 17, 18 and 20-37, which had been included in Groups IV-VIII in the restriction requirement of February 28, 2001, have now been deleted without prejudice toward the continuation of prosecution thereof in one or more divisional applications. The restriction requirement is still traversed with respect to Groups I-III for the reasons of record. It is still hoped that the examiner will examine all of the claims

now present in the case if a linking claim, such as claim 38 is found to be allowable. In any event, applicants explicitly maintain their option to petition this restriction requirement at the appropriate time pursuant to 37 C.F.R. §1.144.

The examiner has continued to require a more descriptive title. Applicants continue to request that this requirement be held in abeyance until allowable subject matter is indicated in the case.

The examiner continues to object to claims 1, 2, 19 and 38-40 as not being limited to the elected species. Applicants continue to request that this objection be held in abeyance until allowable subject matter is identified and/or until after a decision on any petition that applicants may file from the restriction requirement.

The examiner continues to maintain the rejection of claims 1, 2 and 38-40 under the judicially created doctrine of obviousness-type double patenting. Applicants continue to request that this objection be held in abeyance until all other issues are resolved.

Claims 1, 2, 4-8, 19 and 38-40 have been rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the broadly claimed method, for the reasons of record. In response to applicants' arguments, the examiner first states

that the issue relating to the proper interpretation of the terms "preventing" and "inhibiting" would be overcome by changing the terms "preventing" and "inhibiting" to "reducing".

Secondly, with respect to applicants arguments about administration of other NS-specific activated T cells than MBP-activated T cells, the examiner states that the argument is not convincing because the administration of MOG is not shown in the specification to activate T cells *in vitro*. The examiner states that undue experimentation would be required of the skilled artisan to sensitize T cells to every nervous system antigen and administer the cells to an individual to reduce any type of neuronal degeneration. The examiner states that the present invention is unpredictable and complex wherein one skilled in the art may not necessarily prevent, inhibit or reduce any kind of neuronal degeneration in the central nervous system or peripheral nervous system comprising administering all types of NS-specific activated T cells.

Thirdly, the examiner has not found applicants' arguments to be persuasive concerning oral administration as the T cells are only taught to be administrable intraperitoneally. This rejection is respectfully traversed.

As to section (i) of the examiner's comments, the claims have now been amended to change the terms "preventing"

and "inhibiting" to read "reducing", as suggested by the examiner. Accordingly, it is believed that this part of the rejection has now been overcome.

With respect to section (ii) of the rejection, the examiner's attention is invited to the attached declaration of Prof. Michal Schwartz (also known as Michal Eisenbach-Schwartz), who is an inventor of the present application. In this declaration, Prof. Schwartz sets forth experiments using another NS-specific antigen which, when used to activate T cells, also has positive results as predicted in the present specification. These experiments not only show that active vaccination with Nogo-A-derived peptide provides neuroprotection, but also show that the corresponding passive administration of T cells directed against Nogo-A-derived peptide also provides neuroprotection. Thus, these experiments not only confirm statements in the present specification that T cells activated by other NS-specific peptides will be neuroprotective, but also confirm that, if active vaccination provides neuroprotection, passive vaccination will also provide neuroprotection, as is stated in the present specification.

In paragraph 7 of the declaration, Prof. Schwartz further states with respect to active vaccination with MOG, as described in Example 8.2 of the present specification, that

this experiment would cause one of ordinary skill in the art reading the present specification and the experiments described previously in the declaration, to expect that that the concomitant passive vaccination with MOG-activated T cells would also be neuroprotective.

Accordingly, three examples are of record establishing that vaccination with T cells activated by three different NS-specific antigens are all successful or expected to be successful in reducing neurodegeneration. Therefore, one of ordinary skill in the art would be able to conclude that T cells activated by any NS-specific antigen can also be operable for the reasons detailed in the present specification. No experimentation is invited. T cells activated with any NS-specific antigen are expected to be operable for the reasons described in the specification. As this genus is supported by three diverse species, it is urged that applicants are entitled to the generic claims. There is no longer credible reason to believe that the present invention will not be operable with T cells activated by any NS-specific antigen. Reconsideration and withdrawal of this part of the enablement rejection are, therefore, also respectfully urged.

With respect to part (iii) of the rejection, claim 1 has now been amended to specify that when the active

ingredient is activated T cells, they are administered intraperitoneally. Accordingly, this part of the rejection has now been obviated. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 38 and 39 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite in that they are incomplete for omitting essential steps, such omission amounting to a gap between the steps. The examiner states that the omitted steps are the administration of MPB-activated T cells. This rejection is respectfully traversed.

In this rejection, the examiner refers to MPEP §2171.01. This section refers to the omission of matter "disclosed to be essential to the invention as described in the specification or in other statements of record" and that "[s]uch essential matter may include missing elements, steps or necessary structural cooperative relationships of elements described by the applicant(s) as necessary to practice the invention." The examiner states that the omission of the administration of MBP-activated T cells is the omission of an essential step, but the examiner has not explained where the present specification or any other argument indicates that the administration of MBP-activated T cells is an essential step.

Claim 38 requires that NS-specific activated T cells be caused to accumulate at the site of neuronal degeneration.

However, the present specification does not state that, in order for this to occur, it is essential that MBP-activated T cells be administered. In fact, the specification clearly states, in the paragraph bridging pages 30 and 31, that the effects of CNS or PNS injury or disease that result in NS degeneration can be prevented or inhibited by administering an NS-specific antigen or a peptide derived therefrom or a derivative thereof so as to activate T cells *in vivo* to produce a population of T cells that accumulate at the site of injury or disease of the CNS or PNS. Thus, *in vitro* activation of the T cells and administration thereof is not an essential step to cause a population of T cells to accumulate at the site of injury or disease. Clearly, the T cells may be activated *in vitro* and then administered or they may be activated *in vivo* by administering a NS-specific antigen. Claim 38 is intended to be generic to either *in vivo* or *in vitro* activation of the T cells. Thus, the administration of activated T cells is not an essential step and the claims comply with the second paragraph of 35 U.S.C. §112.

Furthermore, there is nowhere disclosed in the specification that it is essential to use MPB as the NS-specific antigen. Indeed, the specification indicates that any antigen obtained from NS tissue may be used (see the first full paragraph on page 31). The issue of enablement is

totally separate from the issue of definiteness, regardless of whether or not other NS-specific antigens are supported by an enabling disclosure. The examiner cannot take the position that applicants have disclosed in the specification that MPB is essential to the invention. Without such a disclosure by applicant, MPEP §2172.01 is inapplicable. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1, 4-6, 8 and 38-40 have been rejected under 35 U.S.C. §102(b) as being anticipated by Popovich. The examiner states that Popovich teaches the intravenous administration of MPB-activated allogeneic T cells into naïve recipient rats. This is done in order to produce an experimental autoimmune disease, EAE.

Claim 1 has now been amended to clarify that the method is a method for reducing neuronal degeneration. None of the present claims now read on the examiner's broad interpretation of "preventing". Furthermore, the claims have been amended to read that the individual to whom the active ingredient is administered is one suffering from an injury or disease involving neuronal degeneration. The mice of Popovich are naïve mice. Accordingly, the present amendments clearly avoid anticipation. The present claims would not be obvious from any reading of Popovich because there is no suggestion by Popovich that MPB-activated T cells will have any

neuroprotective effect. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claim 19 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Popovich in view of Hay. The examiner states that Popovich teaches the intravenous administration of MBP-activated T cells into naïve recipient rats and that Hay teaches that national cell banks have been established for the provision of human cells and tissues to clinicians and research scientists. The examiner considers it obvious to store the activated allogeneic rat T cells of Popovich in a cell bank as taught by Hay. This rejection is respectfully traversed.

First of all, the teachings of Popovich have nothing whatsoever to do with human medicine. As there is no utility in inducing a disease in humans, there would be no reason for one of ordinary skill in the art to put human MBP-activated T cells into a cell bank. Furthermore, Hay provides no reason why one of ordinary skill in the art would want to keep rat T cells in a cell bank. Rat cells can be obtained fresh at any time and are not necessary for current transplantation and biomedical research.

Furthermore, claim 19 has now been amended to specify that the T cells are obtained from a human individual who is not suffering from neuronal degeneration and that the T

cells are stored for future use in the case that the individual from whom the T cells were originally obtained sustains an injury or contracts a disease of the nervous system involving neuronal degeneration. As Popovich does not disclose human cells and provides no motivation to use any process with human cells, no combination of Popovich or Hay can teach or make obvious the method of claim 19. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Roger L. Browdy
Registration No. 25,618

RLB:rd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\Eis-Schwartz2\Pto\AmendmentC.doc

Version with Markings to Show Changes Made

In the Claims

Claims 1-15, 19, and 38 have been amended as follows:

1 (~~Amended~~Twice-amended). A method for ~~preventing or inhibiting~~reducing neuronal degeneration in the central nervous system or peripheral nervous system ~~to ameliorate the degenerative effects~~ of an individual suffering from an injury or disease involving neuronal degeneration, comprising administering to ~~an~~ the individual ~~in need thereof~~having such an injury or disease at least one active ingredient selected from the group consisting of

(a) nervous system (NS)-specific activated T cells;

(b) a NS-specific antigen;

(c) a peptide derived from a NS-specific antigen;

(d) a nucleotide sequence encoding a NS-specific antigen; and

(e a nucleotide sequence encoding a peptide derived from a NS-specific antigen,

thereby causing NS-specific activated T cells to accumulate at the site of injury or disease and ~~prevent or inhibit~~to reduce neuronal degeneration at that site,

wherein, when said active ingredient is NS-specific T cells, said administration is intraperitoneal,

with the proviso that when the disease being ameliorated is an autoimmune disease, the NS-specific antigen is not an autoimmune antigen involved in that disease and said T cells are not activated against an autoimmune antigen involved in that disease.

2 (Amended). The method according to claim ~~1~~ 41, wherein the injury is selected from the group consisting of spinal cord injury, blunt trauma, penetrating trauma, hemorrhaging stroke, and ischemic stroke.

3 (Amended). The method according to claim ~~1~~ 42, wherein the disease is selected from the group consisting of diabetic neuropathy, senile dementia, Alzheimer's disease, Parkinson's disease, facial nerve palsy, glaucoma, Huntington's chorea, amyotrophic lateral sclerosis, non-arteritic optic neuropathy, and vitamin deficiency.

4 (Twice-amended~~Amended~~). The method according to claim ~~1~~ 43, wherein said NS-specific activated T cells are selected from the group consisting of autologous T cells, allogeneic T cells from related donors, and human lymphocyte ~~antigens~~ antigen (HLA)-matched or partially matched semi-allogeneic or fully allogeneic donors.

5 (Amended). The method according to claim ~~4~~ 7, wherein said autologous T cells have been sensitized to human NS antigen.

6 (Amended). The method according to claim 5, wherein said T cells have previously been taken from an individual, have been sensitized to human NS antigen, and then have been stored for future use.

7 (Amended). The method according to claim 4, wherein said NS-specific activated T cells are autologous T cells.

8 (Amended). The method according to claim 4, wherein said T cells are semi-allogeneic T cells.

9 (Amended). The method according to claim ~~1-~~44 wherein said NS-specific antigen is selected from the group consisting of myelin basic protein, myelin oligodendrocyte glycoprotein, proteolipid protein, myelin-associated glycoprotein, S-100, β-amyloid, Thy-1, P0, P2, and neurotransmitter receptors.

10 (Amended). The method according to claim ~~1-~~45 wherein said active ingredient is a peptide derived from a NS-specific antigen ~~is~~ selected from the group consisting of immunogenic epitopes of said antigen and cryptic epitopes of said antigen.

11 (Amended). The method according to claim 10, wherein said peptide is an immunogenic epitope or a cryptic epitope derived from myelin basic protein.

12 (Amended). The method according to claim 10, wherein said peptide corresponds to at least one of the sequences selected from the group consisting of p11-30, p51-70, p91-110, p131-150, and p151-170 of myelin basic protein.

13 (Amended). The method according to claim ~~1~~ 45, wherein the NS-specific antigen or peptide derived ~~therefore~~ therefrom is administered intravenously, intraperitoneally, orally, intranasally, intrathecally, intradermally, topically, or bucally.

14 (Amended). The method according to claim 13, wherein said mucosal administration is selected from the group consisting of oral, intranasal, buccal, vaginal, and rectal administration.

15 (Amended). The method according to claim ~~1~~ 45, wherein said active ingredient is myelin basic protein and is administered orally.

19 (~~Amended~~Twice-amended). A method for providing T cells for future use, comprising:

obtaining T cells from ~~an~~ a human individual who is not suffering from an injury or disease involving neuronal degeneration;

activating said T cells against at least one nervous system antigen; and

storing said activated T cells in a cell bank of T cells that have been activated against a nervous system antigen, for future use in the case that the individual from whom the T cells were originally obtained sustains an injury or contracts a disease of the nervous system involving neuronal degeneration.

38 (~~New~~Amended). A method for ~~inhibiting~~ reducing neuronal degeneration in the central nervous system or peripheral nervous system of an individual ~~in need thereof~~suffering from neuronal degeneration, comprising causing NS-specific activated T cells to accumulate at the site of neuronal degeneration in the individual, ~~in need~~ thereby ~~inhibiting~~ reducing neuronal degeneration at that site, with the proviso that when the individual has an autoimmune disease, said T cells are not activated against an autoimmune antigen involved in that disease.

Claims 17, 18 and 20-37 have been deleted.

Claims 41-46 have been added.

12 (Amended). The method according to claim 10, wherein said peptide corresponds to at least one of the sequences selected from the group consisting of p11-30, p51-70, p91-110, p131-150, and p151-170 of myelin basic protein.

13 (Amended). The method according to claim ~~1-45~~, wherein the NS-specific antigen or peptide derived ~~therefore~~ therefrom is administered intravenously, intraperitoneally, orally, intranasally, intrathecally, intradermally, topically, or bucally.

14 (Amended). The method according to claim 13, wherein said mucosal administration is selected from the group consisting of oral, intranasal, buccal, vaginal, and rectal administration.

15 (Amended). The method according to claim ~~1-45~~, wherein said active ingredient is myelin basic protein and is administered orally.

19 (~~Amended~~Twice-amended). A method for providing T cells for future use, comprising:

obtaining T cells from ~~an~~ a human individual who is not suffering from an injury or disease involving neuronal degeneration;

activating said T cells against at least one nervous system antigen; and